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REMARKS

Applicants thank the Examiner for the courtesy extended to Applicants' attorney during the discussion on December 11, 2003, in the above-identified application. During the discussion, Applicants' attorney noted that Claim 29 was not addressed in the Office Action and that various arguments were not responded to in the Office Action. Applicants' attorney also queried whether the Examiner believed any of the disclosed subject matter was patentable. The discussion is summarized and expanded upon below.

As recited in Claim 25, the present invention is an oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by a method of applying a thermoplastic coating and binding agent in a hot-melt liquid state at a temperature of 100-150°C to said oral or dermal medicinal composition, followed by cooling to solidify the thermoplastic coating and binding agent, wherein said thermoplastic coating and binding agent consists essentially of a mixture of, based on 100% by weight of A and B:

A) a thermoplastic acrylic plastic with a melting temperature above room temperature and below 200°C, a glass transition temperature below 120°C, and a melt viscosity of 1,000 to 1,000,000 Pa-sec at the melting temperature; and

B) 20-50 wt.% of glycerol monostearate, wherein the glass transition temperature of the mixture is no more than 20°K below the glass transition temperature of component A.

The Declaration under 37 C.F.R. § 1.132 of named co-inventor Manfred Assmus, filed June 21, 1999 (first Assmus Declaration), and the Supplemental Declaration of Assmus, filed October 5, 1999 (supplemental first Assmus Declaration), demonstrate the significance of a number of the above-recited limitations.

The first Assmus Declaration demonstrates that the combination of a thermoplastic acrylic plastic within the terms of component A, combined with amounts of glycerol monostearate (GMS), now flow improver component B, in amounts from 20 to 80 wt% of GMS, based on the combination of components A and B, when heated to a temperature of 60°C, 65°C, or 80°C respectively, does not produce an (absolutely) clear and homogeneous melt, such as obtained with a temperature of at least 100°C, as required by the present claims. In addition, the first Assmus Declaration shows that the properties of the product produced, and thus the product itself, changes both by the relative amount of GMS present and the temperature at which the thermoplastic coating and binding agent is applied. The supplemental first Assmus Declaration shows how the heating temperature for, *inter alia*, 50% GMS and 80% GMS, affects the structure of the polymer particles produced. The results show no interaction between the GMS flow improver and the polymer at 65°C; the beginning of interaction at 100°C; and strong interaction at 150°C.

The above-discussed data could not have been predicted by the applied prior art.

Prior to discussing the rejections of record, the Examiner, in the Office Action, refers to findings by the Board of Patent Appeals and Interferences (Board) regarding the First Assmus Declaration and the Supplemental First Assmus Declaration. However, those findings were with regard to claimed subject matter different from that claimed herein, and different prior art rejections from those made herein. The Board obviously has made no findings regarding the presently-claimed invention or the present rejections.

The Examiner finds that "[t]he melt-mixing temperature of 65°C is not representative of the closest prior art value of 100°C for [Yajima et al, discussed *infra*] (cols. 5-7, Examples 4, 7 and 13) as well as 95°C and 100°C for [Deleuil et al, discussed *infra*] (col. 5-6, Table 1, Tests 1-5) wherein the 100°C value is within the claimed range of from 100-150°C."

In reply, by simply picking out temperatures from Yajima et al and Deleuil et al, the Examiner ignores other disclosure in these references that put these temperatures in context. At any rate, to the extent an inventor is required to show unexpected results over prior art, that prior art must actually exist. *E.g.*, *In re Geiger*, 815 F.2d 686, 689, 2 USPQ2d 1276, 1279 (Fed. Cir, 1987) (Newman, J., concurring) ("The applicant is not required to create prior art, nor to prove that his invention would have been obvious if the prior art were different than it actually was"); *In re Chapman*, 357 F.2d 418, 422, 148 USPQ 711, 714 (CCPA 1966) (Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 "would be requiring comparison of the results of the invention with the results of the invention.")

Thus, the Examiner may not ignore other relevant disclosures in Yajima et al and Deleuil et al, as part of the Examiner's burden to consider the subject matter *as a whole*, as required by 35 U.S.C. § 103.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over the abstract of the article *Drugs Made in Germany* (Petereit et al), is respectfully traversed. Petereit et al discloses fast disintegrating controlled release tablets from coated particles, wherein the coating is provided with aqueous dispersions of methacrylic acid and methacrylic ester copolymers, including various Eudragit brand products. Petereit et al further discloses the admixture of 25-50% of tableting excipients and other components. Under the second "IT", GMS is listed among a relatively large number of materials, including various Eudragit brand materials.

The Examiner has interpreted the above-discussed disclosure in Petereit et al as inclusive of pharmaceutical particles coated with a Eudragit brand copolymer and from 25-50% of GMS. Applicants respectfully disagree with the Examiner's interpretation. The

Examiner assumes that all of the materials listed under the second IT each represent a singular component present in an amount of 25-50% of a coating composition. This is clearly incorrect, since various Eudragit brand products are listed therein as well. Rather, the materials listed under the second IT appear to be materials described in the complete article of which Petereit et al is only an abstract. Petereit et al neither discloses nor suggests a coating containing 25-50% by weight of GMS.

In the present Office Action, the Examiner finds that Petereit et al makes a distinction between the Eudragit copolymers and the tableting excipients, fillers and disintegrants as additives, which the Examiner finds embrace GMS. In reply, GMS is simply listed as a material presumably described in the full Petereit et al article, without any further description of how it is used or in what amounts.

During the above-mentioned discussion, the Examiner suggested that the entire Petereit et al article should be consulted. In reply, the burden is on the Examiner to produce the entire article, when the cited abstract is, at best, ambiguous. The abstract of Petereit et al simply does not disclose or suggest the presently-claimed invention, for reasons above stated. Nevertheless, **submitted herewith** is a copy of the entire Petereit et al article, which uses amounts of GMS in amounts much smaller than the presently-recited amounts. Specifically, GMS is listed under 2.1.2. *Excipients*. In Table 1, GMS is used in Examples 5, 7 and 9 with various Eudragit brand products, wherein the number, such as 30D, refers to a dispersion with the numerical polymer content, as described in 2.1.3. *Film formers*. However, in Table 1, the "Dry lacquer substance" is shown, meaning that the GMS concentration per total Eudragit brand polymer is 8.8% in Example 5; 3.3% in Example 7, and 3.0% in Example 9. In addition, Petereit et al is concerned with spray coating formulations, not hot melt preparations.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,707,646 (Yajima et al), is respectfully traversed. Yajima et al discloses a taste masking pharmaceutical composition obtained by melting a substance having a low melting point under heat at a temperature equal to or higher than the melting point thereof, dispersing or dissolving a functional polymer compound in the resultant molten substance to form a composition, melt- or heat-granulating the composition and an unpleasantly tasting basic drug to form a complex and incorporating sugar alcohol and basic oxide to the complex (column 2, lines 25-37). Yajima et al lists various Eudragit brand polymers as the functional polymer (column 2, lines 59-61), and GMS as among preferred substances having a low melting point (column 3, lines 5-6). Yajima et al further discloses that the amount of the functional polymer in the complex is 1-60% by weight, and that the amount of the complex in the composition is 20-60% by weight. While Yajima et al discloses further the percentages of other ingredients, no percentage range is described for the low melting point substance. The Examiner particularly relies on Examples 4, 7 and 13, all of which describe the combination of Eudragit E and GMS. However, in Examples 4, 7 and 13, the percentage of GMS, based on the total amount of GMS and Eudragit E, is 600/700 × 100, or about 86%. Without the present disclosure as a guide, there would have been no motivation to adjust the relative amounts of GMS and Eudragit E in Yajima et al so that the amount of GMS is present as 20-50% by weight of the combination. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration. While the Examiner holds that it would have been obvious to employ the GMS of Yajima et al

within the presently-recited range "for low levels of the drug," no nexus is evident in Yajima et al regarding relative amounts of low melting point substance and functional polymer compound vis-à-vis the amount of drug.

In the Office Action, the Examiner makes certain calculations from Example 4 of Yajima et al, and finds that the GMS amount is 23%. However, it is clear that this amount is based on the **entire** mixture prior to fluidized granulation with water, described therein, rather than a percentage based on the combination of GMS and the Eudragit material alone. Indeed, it is quite clear from Example 4 that 600 g of GMS are mixed with 100 g of Eudragit. Thus, the Examiner's calculation of 23% is both incorrect and irrelevant.

In addition, in not responding to all of the above arguments, the Office Action is incomplete, since 37 CFR 1.104(b) requires that it be complete "as to all matters."

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,188,838 (Deleuil et al) in view of Chemical Abstracts[1], is respectfully traversed. Deleuil et al is drawn to a process for converting into pearl form a pharmaceutical active substance exhibiting an indefinite crystallization point, which is mixed with one or more pharmaceutical excipients in molten form, the melt is forced to pass through a nozzle which is subject to vibration, the pearls formed are allowed to fall in a tower counter current-wise to a gas, and the solid pearls are collected in the bottom of the tower (column 2, lines 12-20). Such active substances thus exhibit a supercooling phenomenon. Deleuil et al discloses a long list of additives which enable the crystallization of the supercooled product to be

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[1] That the new prior art is not listed in the statement of the rejection is irrelevant; reliance thereon is all that is necessary. "Where a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of rejection." *In re Hoch*, 166 USPQ 406, 407 n.3 (CCPA 1970). See also MPEP 706.02(j).

induced, such as "glycerol stearate" marketed under the mark Precirol (column 2, lines 43-44), and as shown in Table 1 in Tests 1-5, in an amount from 25-50%. (Pöllinger et al, *infra*, discloses that Precirol is a mixture of mono-, di- and tri-esters of palmitic acid and stearic acid with glycerol, at column 6, lines 20-21.) Deleuil et al discloses further that it is sometimes desirable to add polymers which are soluble or dispersible in the melt, which will permit a completely controlled and adjustable dissolution of the pearls when they are used, among which polymers are included acrylic resins such as Eudragit brand resins (column 3, lines 15-23). None of the examples in Deleuil et al employ any acrylic resin. However, Test 10 uses ethyl cellulose in an amount of 3.5%, which ethyl cellulose is disclosed as an applicable polymer (column 3, lines 20-22). Thus, to the extent Deleuil et al discloses the combination of an additive and a polymer, the additive, e.g., Precirol, which according to Pöllinger et al contains GMS in some undefined amount, would be present in significantly greater amounts than the additive, e.g., Eudragit brand polymer. Without the present disclosure as a guide, one skilled in the art would not have selected the presently-recited components A and B in the relative amounts required by the present claims. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

In the Office Action, the Examiner now relies on Chemical Abstracts to support his finding that the "glycerol stearate" described in Deleuil et al is GMS. In reply, Chemical Abstracts does not support the Examiner's finding that Precirol (Special WL 2155) is GMS. Rather, RN 8067-32-1 refers to "octadecanoic acid, ester with 1, 2, 3-propane triol

hexadecanoate", and RN 11099-07-3 refers to "octadecanoic acid, ester with 1, 2, 3-propane triol." Obviously, such an ester could be a mono-, di-, and/or tri-ester, and indeed, Pöllinger et al, discussed above, suggests that it is a mixture of mono-, di-, and tri-esters.

The Examiner has improperly ignored the remaining arguments over Deleuil et al and thus again, fails to comply with 37 CFR 1.104(b).

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,603,957 (Burguiere et al) in view of U.S. 5,552,159 (Mueller et al) is respectfully traversed. Burguiere et al discloses controlled-release microcapsules of acetylsalicylic acid, containing a coating which is obtained from a coating composition comprising at least one film-forming polymer insoluble in the gastrointestinal environment (column 5, lines 44-45), such as a Eudragit brand polymer (column 6, lines 7-13), in an amount of 60-85% by weight (column 5, line 56); at least one water-soluble polymer; at least one solid lubricating filler; and at least one hydrophobic plasticizer, which may be a stearate of a glycol such as glycerol (column 6, lines 33-36), which plasticizer is present in an amount of 2-20, preferably 5-15, wt% (column 5, line 60). Burguiere et al further discloses that their microcapsules are obtained by a process consisting essentially of preparing the coating composition components by mixing them in a solvent system, applying the mixture to particles of acetylsalicylic acid, drying the resulting microcapsules, and if appropriate, mixing the latter with at least one anti-caking agent (column 7, lines 14-21). Mueller et al discloses a solid depot drug form comprising a pharmaceutical active ingredient and a polymer melt comprising at least one water-insoluble poly(meth)acrylate with a glass transition temperature in the range from -60° to 180°C such as a Eudragit brand polymer, and either a particular water-soluble hydroxyalkyl cellulose or hydroxyalkylmethyl cellulose or an N-vinylpyrrolidone polymer.

While Mueller et al discloses a solid depot drug form produced by melt extrusion at from 50° to 200°C, Mueller et al discloses and suggests nothing with regard to the presently-recited requirement of a hot-melt liquid state at a temperature of 100-150°C, nor the presently-recited GMS, nor the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*.

Without the present disclosure as a guide, one skilled in the art would not have combined Burguiere et al and Mueller et al. Nor could one skilled in the art have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

In the present Office Action, the Examiner simply relies on the findings of the Board. However, as discussed above, the Board made no findings with regard to this rejection or the present claims. Why would one skilled in the art make the controlled-release microcapsules of Burguiere et al any differently from the process disclosed therein, there being no evidence or suggestion that Burguiere et al's process is unsatisfactory?

Nor has the Examiner responded to any of the above-discussed arguments and thus again, fails to comply with 37 CFR 1.104(b).

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,858,412 (Staniforth et al) in view of Mueller et al, is respectfully traversed. Staniforth et al discloses a sustained-release formulation comprising an active ingredient, an augmented microcrystalline cellulose which possesses excellent compressibility, and a sustained-release carrier (column 5, lines 4-15). Staniforth et al discloses further that one or more compressibility augmenting agents may be present (column 6, lines 26-31). Staniforth et al

discloses a wide variety of compressibility augmenting agents, beginning at column 7, line 64, among which are a relatively long list of surfactants, including GMS (column 11, line 33). Staniforth et al further discloses Eudragit brand polymers as applicable sustained release carriers (column 20, lines 29-31). The relatively large numbers of applicable combinations of ingredients in Staniforth et al is so large that it would not have even been *prima facie* obvious to choose the combination of a Eudragit brand polymer and GMS, forgetting about all the other limitations of the present claims. See *In re Baird*, 29 USPQ 2d 1550 (Fed. Cir. 1994) (copy of record).

Mueller and its deficiencies have been discussed above.

Without the present disclosure as a guide, one skilled in the art would not have combined Staniforth et al and Mueller et al. Moreover, even if combined, the result would not have been the presently-claimed invention. See *Baird, supra*. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

In the present Office Action, the Examiner simply ignores the *Baird* precedent, as well as all of the other arguments raised above, contrary to the requirements of 37 CFR 1.104(b).

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over JP 51-91317 (JP '317), U.S. 5,484,608 (Rudnic et al), and U.S. 5,695,784 (Pöllinger et al) in view of Petereit et al, Burguiere et al and Mueller et al, is respectfully traversed. JP '317 discloses

pharmaceutical tablets or granules coated with a composition comprising a particularly specified polymer, a water-insoluble non-ionic surfactant solid at ambient temperature, and a higher fatty acid solid at ambient temperature. GMS is disclosed as a preferred non-ionic surfactant. No amounts of non-ionic surfactant are disclosed. Rudnic et al discloses a sustained-release pharmaceutical composition comprising a highly soluble pharmaceutical agent in a pharmaceutical carrier comprising a hydrophilic polymer, such as a Eudragit brand polymer (column 2, lines 50-61) in a hydrophobic matrix, including GMS (column 2, line 62 ff). While the Examiner relies on Example 1 therein, which contains a matrix component in an amount of 20%, other examples, i.e., Examples 2 and 3, which specifically discloses GMS, contain GMS in an amount of 5%. There is no disclosure or suggestion to use GMS in an amount as high as 20% in Rudnic et al. Pöllinger et al discloses a flavor-masked pharmaceutical composition in the form of microcapsules prepared using specific coatings (column 3, lines 23-27). While Pöllinger et al lists various film-forming agents known in the art (column 4, line 45 ff), only some Eudragit brand, but not all Eudragit brand, polymers may be used in Pöllinger et al (column 4, line 66 ff). For example, Eudragit brand polymers that are cationic did not produce the desired results (column 5, line 44 ff). Pöllinger et al discloses further that plasticides may be included, among which are GMS (column 5, lines 49-57, especially line 53). None of the examples in Pöllinger et al contain GMS and thus, no percentage range therefore is disclosed.

The disclosures and deficiencies of Petereit et al, Burguiere et al, and Mueller et al have been discussed above.

One skilled in the art would not have combined the above-applied prior art without the present disclosure as a guide. Moreover, even if combined, the result would still not be the presently-claimed invention. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of

thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

In the present Office Action, it is clear that the Examiner has taken bits and pieces from the disclosures of the applied prior art, that he believes supports his position, while ignoring disclosure that does not. Clearly, the combination of the six-applied references could be stated to suggest almost anything, but it is only with the present disclosure as a guide that one skilled in the art would come up with the present invention.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over Mueller et al in view of Petereit et al and Burguiere et al, is respectfully traversed. The disclosures and deficiencies of each of these references have been discussed above. First of all, Petereit et al do not disclose the function of the GMS therein. Burguiere et al discloses a maximum of 20% by weight of plasticizer, and preferably a maximum of 15%. A plasticizer is not even required in Mueller et al. Without the present disclosure as a guide, one skilled in the art would not have combined the above-applied references. Moreover, even if combined, the result would still not be the presently-claimed invention. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

In the present Office Action, the Examiner does not even respond to the above arguments, but simply refers to rebuttals of the other rejections. If those rebuttals apply to the present rejection, it is not clear why the present rejection was even made. But, since it was made, and involves a different combination of references, Applicants deserve the Examiner's specific reasoning in rebuttal of the above-discussed arguments regarding this rejection.

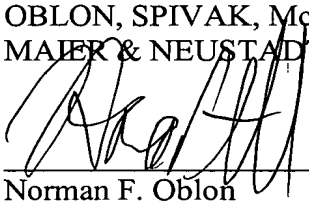
For all the above reasons, it is respectfully requested that this rejection be withdrawn.

Applicants respectfully traverse the finality of the present Office Action. In the amendment filed November 18, 2003, no change was made to any of the claims; only one new claim, i.e., Claim 29, was added. Yet, the Examiner has made two new grounds of rejection, i.e., the rejection under 35 U.S.C. § 103(a) over Petereit et al, and the rejection over Deleuil et al in view of Chemical Abstracts. These rejections were **not** necessitated by Applicants' amendments to the claims, and were clearly not necessitated by the addition of Claim 29, since Claim 29 is not even addressed in the Office Action. In addition, the Office Action is incomplete, by failing to address Claim 29, and by failing to address **all** the arguments made in traversal of the prior art rejections in violation of 37 CFR 1.104(b). Note that by changing the rejection over Petereit et al from § 102 to § 103 and making it Final, Applicants are now foreclosed as a matter of right from presenting evidence of non-obviousness, whereas such evidence would have been irrelevant for the withdrawn rejection under § 102. Accordingly, the Examiner is respectfully requested to withdraw the finality of the Office Action and, if the next Office communication is not a Notice of Allowance, then a new non-final Office Action be entered so that Applicants may respond as a matter of right to the new rejections.

Applicants respectfully submit that all of the presently pending and active claims in this application are now in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Fast Disintegrating Controlled Release Tablets from Coated Particles

K. Lehmann, H.-U. Petereit, and D. Dreher †

Summary

Small particles such as crystals, granules and pellets of a particle size in the range of 0.3–1.2 mm were coated with aqueous dispersions of methacrylic acid and methacrylic ester copolymers (Eudragit RL 30 D, RS 30 D, L 30 D-55 and NE 30 D) for taste masking, resistance to gastric fluid and diffusion controlled sustained release properties and compressed into fast disintegrating tablets. Admixture of 25–50 % of tabletting excipients as microcrystalline cellulose, sorbitol, starch and Na-carboxymethyl starch as fillers, and disintegrants were necessary to get fast disintegration of the tablets; the function of these substances was also filling of the interspace, as well as separation and protection of the coated particles during compression. Some damage of coatings were observed with brittle coating materials when elongation at break was around 20 % only. More flexible films of more than 75 % elongation of break withstand mechanical stress of compression so that the release pattern of disintegrating tablets was very similar or nearly the same as for the uncompressed particles. Examples were given for taste masking of paracetamol, sustained release preparation of potassium chloride and theophylline and also enteric coated acetylsalicylic acid and indometacin. As an alternative to fill coated particles in capsules such fast disintegrating tablets have the advantage of yielding higher drug concentrations, of being safe against criminal manipulations, of being dividable and less expensive in production.

1. Introduction

Solid oral dosage forms with controlled release which disintegrate after application into a large number of subunits, socalled multi-unit dosage forms, show several highly important advantages as compared to monolithic preparations. The small particles are mixed with the contents of the stomach and intestine and distributed over a larger area. Thus high local concentrations of the drug are avoided and the risk of undesired side effects is reduced. The particles should be smaller than approximately 2 mm to be transported continuously together with the food contents through the digestive tract so that the quality, amount and timing of food uptake as well as movement and relaxation time of the body is of minor influence on the drug release [12]. So inter- and intra-individual variations of bioavailability are reduced and more constant blood levels of the drug can be achieved.

Multi-unit dosage forms of controlled release have been formulated with coated particles for many years but in most cases they have been filled into hard gelatine capsules. Such preparations present some severe disadvantages: The capsules themselves are relatively expensive, the bulk density inside the capsule is low so that a larger volume is needed for high doses, and the dose cannot be divided using the usual capsule design. On the contrary tablets can be produced less expensively and due to their higher density they can be swallowed to a weight of approximately 1 g. They can be divided easily without remarkable influence on the drug release which is controlled after disintegration of the tablet by the totality of still intact coated particles.

We had some success with coated granules containing enzymes as early as in 1970 [1]. Further results with coated drug particles

R & D Department/Application Technology, Pharma Polymers, Röhm GmbH, Darmstadt (Fed. Rep. of Germany)

were published in 1976 [2]. Here methaqualone crystals (0.3–0.8 mm Ø) were coated with Eudragit RL/RS 1 : 1 and compressed together with some excipients. After an initial dose of 10 % the drug release curve was nearly parallel to that of the original coated particles. Similar effects were found with slow release acetylsalicylic acid particles [3]. Also fast disintegrating theophylline tablets were described, prepared from granules which were coated with Eudragit NE 30 D; surprisingly the drug release of the granules from disintegrated tablets was something slower: This effect was obviously caused by some agglomeration of the coated drug particles during compression. Further results with these drugs were published in [4].

In the meantime the concept of tabletting coated drug particles has found more interest, especially in the USA, when hard gelatine capsules were manipulated with criminal intent. Compression of taste masked, coated drugs is described by Mehta [7] and France and Leonhard [8]. Sustained release tablets from microcapsules are described by Rottmann [9] where a particle size of 5 to 300 µm is recommended, when particles of 600–1000 µm were completely destroyed during compression. Becker [10] reported that 10–50 % microcrystalline cellulose is required to obtain sufficient protection and good hardness of the tablets.

Now commercially available aqueous dispersions can be mixed [4], giving films of good mechanical properties [5]. Therefore the applicability of tabletting coated particles was investigated in greater detail to support broader application of this technology.

2. Materials and methods

2.1. Raw materials

2.1.1. Drug particles

Paracetamol crystals spherical, particle size 0.3–0.8 mm, Chemische Werke Aubing GmbH, Mannheim; potassium chloride crystals, spherical, particle size 0.3–1.0 mm, Chemische Fabrik Lehrte, Lehrte; theophylline granules Type 0308, particle size 0.3–0.8 mm, theophylline powder Type 200 mesh, Boehringer Ingelheim, Ingelheim/Rhein; acetylsalicylic acid (ASA) crystals spherical, particle size 0.3–1.0 mm, Chemische Werke Aubing, Mannheim (all FRG); indometacin pellets spherical, particle size 0.6–1.25 mm, prepared from indometacin powder (see 2.2.4.).

2.1.2. Excipients

Lactose D20, Meggle, Wasserburg (FRG); methyl cellulose, Methocel® E5, Dow Chemical Intern. GmbH, Frankfurt/Main (FRG); corn starch, Deutsche Maizenawerke GmbH, Hamburg (FRG); microcristalline cellulose, Avicel® PH 102, FMC Export Corporation, Philadelphia, PA (USA); sorbitol, Karion® Instant, E. Merck, Darmstadt; calcium dihydrogenphosphate, Emcompress®, G. Parmentier, Frankfurt/Main; Na-carboxymethyl starch, Explotab®, G. Parmentier, Frankfurt/Main; micronized silica, Siloid® 244 FP, Grace GmbH, Worms; carbosil, Acrosil 200®, Degussa, Frankfurt/Main; talc: E. Merck, Darmstadt; magnesium stearate: E. Merck, Darmstadt; glyceryl monostearate, Imvitor® 900, Hüls AG, Marl (all FRG).

2.1.3. Film formers

Poly(ethylmethacrylate methacrylic acid) 1 : 1 = methacrylic acid copolymer type C USP XXII/NF XVII = Eudragit L 30 D-55[1] (30 % aqueous dispersion) or Eudragit L 100-55 (powder, redispersible). Poly(ethylacrylate, methylmethacrylate) 2 : 1 Polyacrylate Dispersion 30 Per Cent, Ph. Eur. = Eudragit NE 30 D (30 % aqueous dispersion). Poly(ethylacrylat, methylmethacrylate, trimethylammonioethyl-methacrylate chloride) 1 : 2 : 0.2 = ammonio methacrylate copolymer type A USP XXII/NF XVII Suppl. 4 = Eudragit RL 100 (granules) or Eudragit RL 30 D (30 % aqueous dispersion). Poly(ethylacrylate, methylmethacrylate, trimethylammonioethyl-methacrylate chloride) 1 : 2 : 0.1 = ammonio methacrylate copolymer type B USP XXII/NF XVII Suppl. 4 = Eudragit RS 100 (granules) or Eudragit RS 30 D (30 % aqueous dispersion): Röhm GmbH, Darmstadt (FRG).

2.1.4. Plasticizers

Triethyl citrate NF, Eudraflex® Röhm GmbH, Darmstadt; acetyltriethyl citrate: Pfizer GmbH, Karlsruhe; triacetin: BASF AG, Ludwigshafen/Rhein; polysorbate 80 (Tween 80) Atlas Chemie, Essen; polyethylene glycol 6000: Hüls AG, Marl (all FRG).

2.2. Coating of particles, compression to tablets and testing of drug release

2.2.1. Taste masked preparations

Paracetamol crystals were coated with Eudragit NE 30 D in fluid-bed devices as described in [11], p. 161, exercise 3.3.8. When 2 % dry polymer substance of formulation 1 as described in Table 1 was applied, the crystals were tasteless in the mouth for a minimum of 1 min. The process data are described in Table 2, No. 1. A powder mass for tabletting was prepared by

[1] Tradename as from July 1993: Eudragit L 30 D-55, formerly Eudragit L 30 D.

Table 1: Coating formulations for drug particles.

Formulation No.	1	2	3	4	5	6	7	8	9	10
Eudragit-Type										
Dry lacquer substance from										
NE 30 D	4.3	16.7	–	–	–	–	4.5	–	6.5	–
RL 30 D	–	–	3.0	2.0	6.4	–	–	–	–	–
RS 30 D	–	–	9.0	10.0	9.6	–	–	–	–	18.0
L 30 D-55	–	–	–	–	–	15.0	4.5	12.0	6.5	–
Triethylcitrate	–	–	2.4	2.4	3.2	–	0.9	1.2	1.3	–
Acetyltriethylcitrate	–	–	–	–	–	1.5	–	–	–	3.6
PEG 6000	0.4	–	–	–	–	–	–	–	–	–
Talc	7.3	8.3	6.0	6.0	–	7.5	–	6.0	–	–
Pigments	3.8	–	–	–	–	–	–	–	–	–
Siloid[a]	–	–	–	–	–	–	–	–	–	3.6
Polysorbate 80	–	–	–	–	–	–	–	–	0.1	–
Glycerol monostearate	–	–	–	–	1.4	–	0.3	–	0.4	–
Methylcellulose	0.4	–	–	–	–	–	–	–	–	–
Water ad 100.0 in all formulations										

In all formulations 0.1–0.2 silicon antifoam emulsion ASE 2 was used. In some formulations small amounts of 1 N NaOH or citric acid were added dropewise to adjust to pH 5. Formulation No. 7: NaOH and citric acid. Formulation No. 9: NaOH.
[a] Micronized silica (Grace, 244 FP).

Table 2: Coating proocsses for drug particles.

Formulation No.	Drug	Ø (mm)	Batch (kg)	Formulation (kg)	Equipment	Drying air temperature (°C) in/out	Spray pressure (bar)	Spray time (min)	% Coating polymer/all dry substances
1	paracetamol crystals	0.3–0.8	50	23.3	WSG 30	42/30	2.0	145	2/8
2	potassium chloride crystals	0.3–1.0	6	6.7	WSG 5	30/22	2.0	120	14/21
3	theophylline granules	0.3–0.8	50	21	WSG 30	40/20	2.0	80	7/10.5
4	theophylline granules	0.3–0.8	2	1.7	GPCG 1	40/32	2.0	85	10/17
5	theophylline pellets	0.8–1.25	0.75	0.56	Uniglatt	40/24	2.0	80	12/15
6	ASA crystals	0.3–1.0	150	96	WSG 60	60/24	6.0	120	10/16
7	ASA crystals	0.3–1.0	6	4.8	WSG 5	50/31	3.0	84	12/14
8	indometacin pellets	0.5–1.25	1	1.5	Uniglatt	40/23	1.8	160	18/29
9	indometacin pellets	0.5–1.25	0.9	0.8	Uniglatt	50/22	1.8	120	12/14
10	paracetamol crystals	0.3–1.0	150	21.0	WSG 60	50/27	2.0	75	2.5/7.4

mixing the substances of the formulation No. 3 in Table 3. The mixture was compressed on a single punch press EKO (Korsch, Berlin, FRG) with 15–20 kN pressure resulting in tablets with a hardness of 90–100 N. They disintegrate in water or simulated gastric fluid in less than 1.5 min. During this time the tablets disintegrate also in the mouth without release of any bitter taste. By chewing the particles the bitter taste is observed soon. A similar formulation was prepared by using Eudragit RS 30 D. This formulation is given in Table 1 in column 10. The coating process was developed up to a 150 kg scale. The process data are given in Table 2, formulation No. 10. The compositions of mixtures of powders for tabletting with the relevant excipients are given in Table 3, formulation No. 2, the galenical data of the tablets in Table 4, No. 10.

Table 3: Excipients for tabletting of coated particles.

Formulation No.	1	2	3	4	5
Coated drug particles	73.7	53.3	64.5	49.5	60.0
Microcrystalline Cellulose	20.0	15.0	30.0	35.0	34.5
Sorbitol	–	–	–	10.0	–
Calcium hydrogen phosphate[a]	–	27.1	–	–	–
Na-carboxylmethyl-starch[b]	5.0	4.0	4.4	–	5.0
Cornstarch	–	–	–	5.0	–
Talc	1.0	–	0.9	–	–
Carbosil	–	0.1	–	–	–
Mg-stearate	0.3	0.5	0.2	0.5	0.5
	100.0	100.0	100.0	100.0	100.0

[a] Emcopress. [b] Explotab.

The coated crystals were tested in a USP-Paddle apparatus and after 30 min 82 % and after 60 min 95 % of the contained drug was released, from the tablets after 30 min 82–97 % and after 60 min more than 95 %. If the tablets are sucked in the mouth a slightly bitter taste occurs after 30 s.

2.2.2. Particles with time-delayed drug release

Potassium chloride crystals were coated as described in [11], p. 161, with 14 % dry lacquer substance from Eudragit NE 30 D. A SEM (scanning electron microscopy)-photo is given in Fig. 1 and shows the coated crystals in their spherical form and the layer structure of the coating. Process data see Table 2, formulation No. 2. A mixture of powder excipients was formulated as given in Table 3, formulation 1, and was compressed to tablets using a single punch press EKO (Korsch, Berlin, FRG) compression force was in the range of 5–25 kN. For the working conditions on a rotary press Type RP 14 (Horn, Worms, FRG) see Table 5. The drug release from the coated crystals and the disintegrating tablets in water is given in Fig. 2. The release from the tablets in comparison to the coated crystals was only

Table 4: Specification of coated drug particles and tablets.

Formulation No.	Drug	Coating polymer/ dry substance (%)	Drug content (%)	Tablets W (mg)/Ø (mm)/ H (mm)	Drug (mg)	Tabletting pressure (kN)	Hardness (N)	Disintegration time gastric fluid/ water (min)
1	paracetamol crystals	2/8	92	814/18/7.5 (oblong)[a]	490	15–20	94	2/1
2	potassium chloride crystals	14/21	72	600/10/4.5	320	15	98	34/13
3	theophylline granules	7/10.5	89	545/18/7.5 (oblong)[a]	350	10	40	1/1
4	theophylline granules	10/17	83	300/10/2.9	175	10	55	1/1
5	theophylline pellets	12/15	82	610/12/5.0	300	13	67	1/1
6	ASA crystals	10/16	84	300/10/3.2	129	10	158	7/11
7	ASA crystals	12/18	82	600/10/5.6	252	15	135	5/6
8	indometacin pellets	18/29	25	600/18/7.5 (oblong)[a]	75	15–22	17	1/1
9	indometacin pellets	12/14	25	600/18/7.5 (oblong)[a]	75	18–23	58	4/12
10	paracetamol crystals	2.5/7.4	92	600/10/5.5	490	15	60	5/10

Ø = Diameter or length of oblong tablets. [a] Edge height 6.5 mm.

Table 5: Preparation of sustained release potassium chloride tablets on a rotary press.

Specification of tablets:
Rotary press Horn RP 14 H (rotation 25/min)
Form of punches: oblong 18 mm × 7.5 mm
Tablet weight: 1158 mg (± 1.3 %) Drug content calculated: 600 mg per tablet Found: 100.3 % of claim (± 5.3 %)
Hardness: 120 N (± 9.12 %) (compression pressure appr. 20 kN)
Friability (10 min Roche friabilator): 0.3 %
Disintegration time (DAB 9): < 1 min

slightly faster and the influence of the compression force was small. Increase of release rate cannot be correlated to higher compression force. A SEM-photo of a cross section of a tablet is given in Fig. 3. The surface of the particles is covered to a very high extent with tabletting excipients, which also fill the interspace.

Theophylline granules were coated with 5 % dry polymer substance from Eudragit NE 30 D as described in [11], p. 161, exercise no. 3.3.8., in a fluid-bed coater with the formulation No. 2 in Table 1. Process data are given in Table 2 in the line no. 3. A mixture of excipients was made following formulation No. 1 in Table 3. Compressed tablets from this powder mass had a weight of 545 mg and contained 350 mg theophylline; they disintegrated in artificial gastric fluid during 2–3 min. A release test in a paddle apparatus as described in USP XXII Method 2: Rotation rate 5.0 rpm, 2 h in artificial gastric fluid pH 1.3, then buffered to pH 6.8 by addition of the solution of 22 g $Na_3HPO_4 \times 12\ H_2O$ in 100 ml 0.1 HCl. The release rate for theophylline is given in Fig. 4. During the first 2 h the disintegrating tablets show a release rate which is approximately 8 %-scale units higher.

In the same manner also the Eudragit RL/RS 30 D mixtures were used to coat the same theophylline granules as described in the formulations No. 3 and 4 in Table 1, and powder mixtures were compressed as described in formulation No. 1 in Table 2. The release profiles are given in Fig. 5. Preliminary results were already published in [4]. SEM-photos of the surface of the tablets is given in Fig. 6 and a cross section in Fig. 7 and 8.

Theophylline pellets with a particle size of 0.6–1.25 mm were prepared as described in [11], exercise 3.2.1., p. 116, starting from theophylline granules and adding theophylline powder with Eudragit NE 30 D as a binder. These pellets were coated by spraying 12 % solid polymer of a mixture of Eudragit RL 30 D/RS 30 D 4 : 6. Formulation No. 5 in Table 1 was used. Retardation of drug release was achieved for 8 h. The process data are given in Table 2 No. 5. Data of the coated particles and tablets see Table 4, formulation 5.

To prepare fast disintegrating tablets the coated pellets and the excipients given in formulation 5 of Table 3 were mixed. Tablets prepared from this powder mass had a weight of 610 mg equivalent to 300 mg theophylline per tablet. They disintegrate within 1 min in water or simulated gastric fluid. The results of the release test is given in Fig. 9. The release profile of theophylline from the tablets compared with the release from the coated pellets is very similar, only in the region of 4 to 5 h there is a slight reduction of release rate of the tablets of approximately 5 %-scale units. The SEM-photo of the cross section in Fig. 10 shows that the pellets after compression are very well preserved.

2.2.3. Enteric coated particles

Acetylsalicylic acid (ASA) crystals were coated in a fluid-bed device as described in [11], exercise No. 3.3.7., p. 156. The formulation with Eudragit L 30 D-55 is given in Table 1 under No. 6 and was reproduced several times in 150 kg scale.

The mixture of Eudragit L 30 D-55 and NE 30 D in a laboratory scale for the formulation No. 7 in Table 1 was prepared in the following way: Eudragit L 30 D-55 was brought to pH 5 by adding dropwise 1 N sodium hydroxide solution under continuous stirring and was then mixed with aqueous polysorbate solution. Eudragit NE 30 D was modified separately by adding diluted citric acid until pH 5 was reached. Talc was suspended separately in water, also adapted to ph 5 and antifoam emulsion added. Then the three separately prepared mixtures were mixed

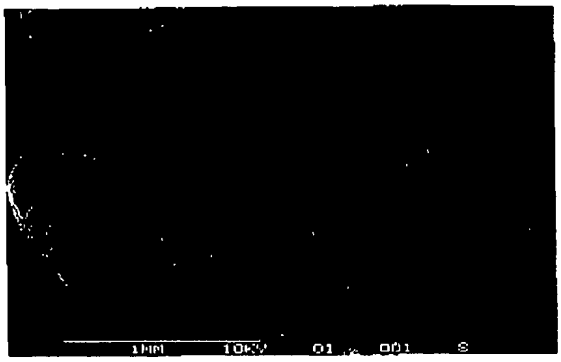

Fig. 1: Spherical KCl crystals coated with 14 % polymethacrylate dispersion Eudragit NE 30 D.

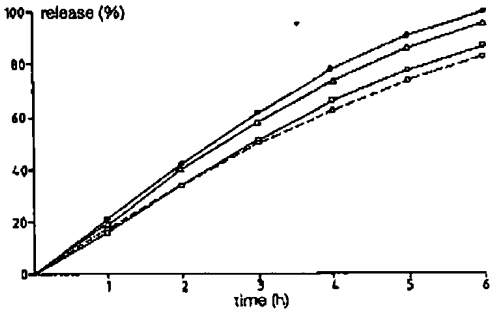

Fig. 2: Fast disintegrating tablets of KCl crystals coated with Eudragit NE 30 D (14 %). Compression force: ● = 15 kN; Δ = 5 kN; □ = 25 kN; tablets from coated crystals; ○ = coated crystals.

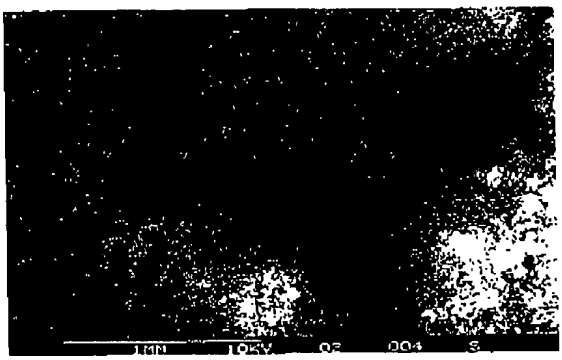

Fig. 3: Cross section of KCl tablets prepared from coated particles of Fig. 1.

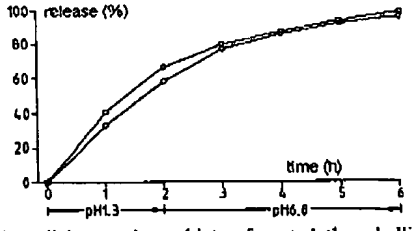

Fig. 4: Fast disintegrating tablets of coated theophylline granules. Coating 5 % dry polymer substance from Eudragit NE 30 D. □ = Disintegrating tablets; ○ = coated granules.

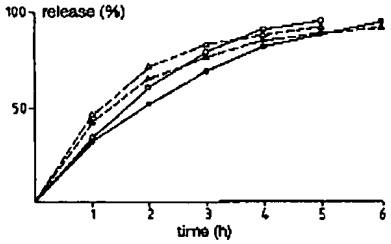

Fig. 5: Fast disintegrating tablets from theophylline granules coated for sustained release with 10 % Eudragit RL/RS. △ = Granules, ○ = tablets; RL : RS = 1 : 3; ▲ = granules; ● = tablets; RL : RS = 1 : 5.

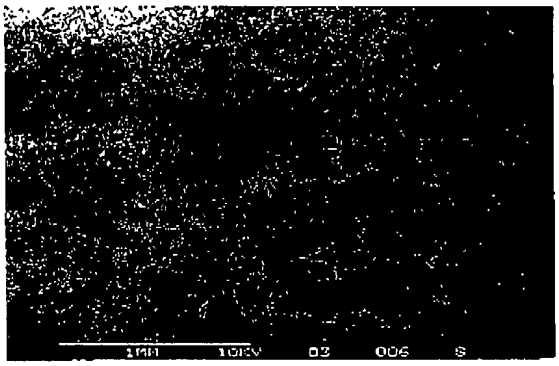

Fig. 6: Surface of theophylline tablets from coated granules of formulation 1 of Table 3.

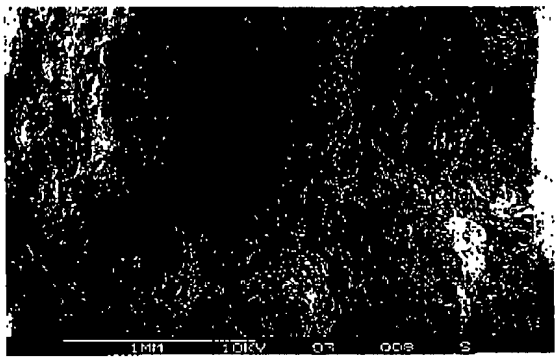

Fig. 7: Cross section of theophylline tablets of formulation 1 of Table 3.

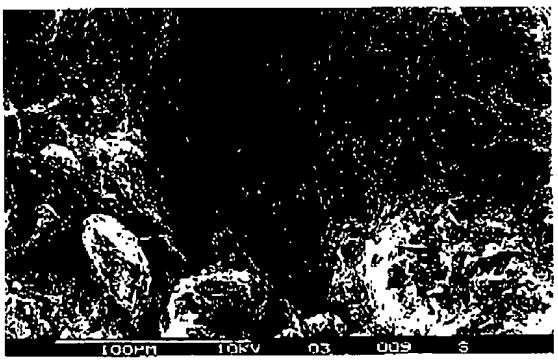

Fig. 8: Cross section of theophylline tablets of Fig. 7 in higher magnification.

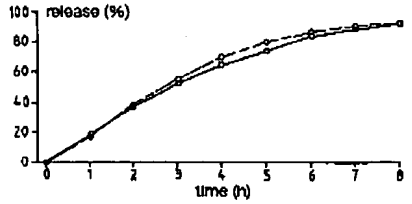

Fig. 9: Fast disintegrating tablets from coated theophylline pellets. Coating 12 % dry polymer substance from Eudragit RL 30 D/RS 30 D 4 : 6. □ = Disintegrating tablets; ○ = coated pellets.

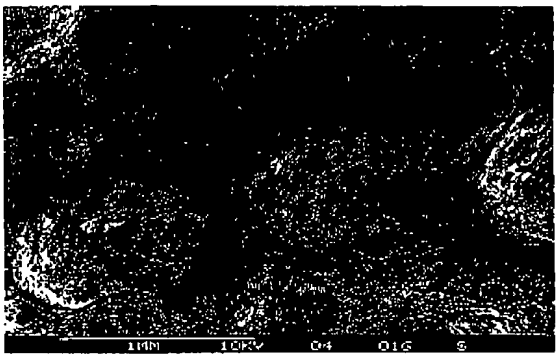

Fig. 10: Cross section of tablets containing theophylline pellets coated with Eudragit RL/RS 4 : 6 and excipients of formulation 5 of Table 3.

in the given order. 12 % dry polymer substance was applied as given in Table 2. No. 7. This was equivalent to 18 % of total solid substances in the coating so that the coated particles contained 82 % ASA. The release was tested in the USP-Paddle-apparatus. After 2 h treatment in gastric fluid the undissolved material was filtered and resuspended in artificial intestinal fluid USP pH 6.8. The analytical determination of released ASA was made with the UV-method USP XXI. p. 1972, "Aspirin delayed-release capsules". The release rate from the coated crystals is given in Fig. 11, curve II. The same release profile was obtained with particles coated with the formulation No. 6 in Table 1 when Eudragit L 30 D-55 alone was used.

2.2.3.1. Tabletting of enteric-coated ASA particles

The coated ASA crystals were mixed with excipients following formulation No. 4 in Table 3 so that a free flowing, good compressible powder mass was obtained. The mixture was compressed to tablets as described in Table 4 under No. 6 and 7. The release profiles are given in Fig. 11 in comparison to the release of ASA from coated crystals. Curve III shows the release from tablets of particles coated with a mixture of Eudragit L 30 D-55 and NE 30 D-55 (formulation No. 7 in Table 1). Curve I shows the release from similar tablets, which contain particles coated with Eudragit L 30 D-55 only (formulation No. 6 in Table 1). In this case cracks occur in many places of the coated particles. The reason is that Eudragit L 30 D forms very brittle films which cannot withstand the compression forces. Such cracks can be seen in Fig. 13. It is clear that such preparation will release some ASA immediately in the stomach (Curve I, Fig. 11). The SEM-photo Fig. 12 was made with crystals coated with a mixture of Eudragit L 30 D-55/NE 30 D and shows deformation of surface areas by the compression forces, but no formation of cracks.

2.2.4. Indometacin pellets

Indometacin pellets 0.6–1.2 mm ∅ were prepared in a coating pan from saccharose crystals 0.5–0.8 mm ∅ by adding a mixture of indometacin and lactose-powder 1 : 1 as described in [11] exercise 3.2.1., p. 116. The pellets were coated with the formulations No. 8 and 9 in Table 1. The amounts of coating mat-

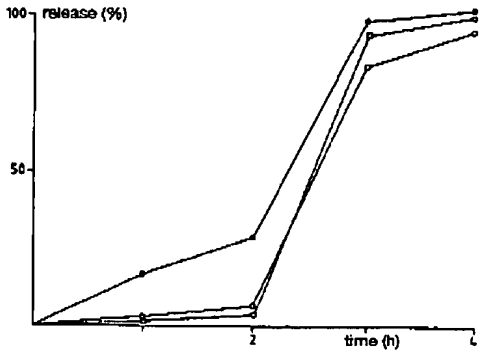

Fig. 11: Fast disintegrating tablets from enteric coated ASA crystals. ● (I) = Tablets from crystals coated with 10 % polymer dry substance from Eudragit L 30 D-55; □ (II) = crystals coated with 12 % dry polymer substance from Eudragit L 30 D-55/NE 30 D 1 : 1; ○ (III) = tablets from coated crystals II/disintegration time max. 8 min.

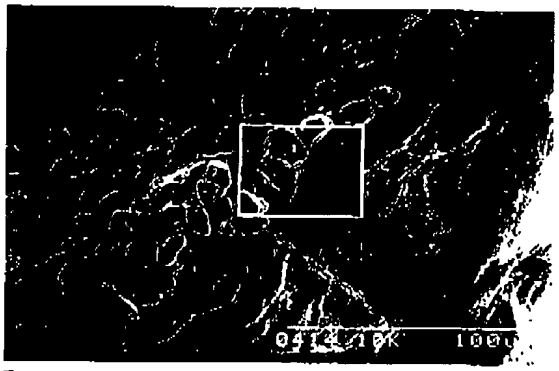

Fig. 13: ASA particles coated with Eudragit L 30 D-55 cross section showing formation of cracks during tabletting due to high brittleness of film forming material.

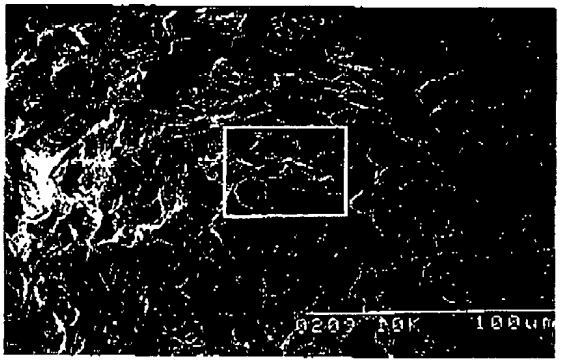

Fig. 12: ASA particles coated with a mixture of dispersions Eudragit L 30 D-55/NE 30 D cross section of the tablet. Deformation of film by starch particles without any formation of cracks.

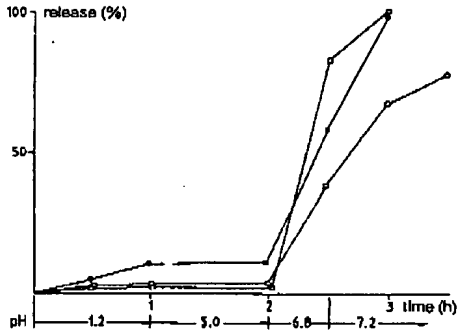

Fig. 14: Fast disintegrating tablets from enteric coated indometacin pellets. □ (I) = Coated pellets; ● (II) tablets (L 30 D-55); ○ (III) = tablets (L 30 D-55/NE 30 D 1 : 1).

erials and process data are given in Table 2 under No. 8 and 9. The general procedure was the same as given above for ASA. The mixing ratio with tabletting excipients is given in formulation No. 4 in Table 3. The data for compression to fast disintegrating tablets can be taken from Table 4 No. 8 and 9.

In the usual USP-paddle test only dissolved drug is measured as released, when the digestive fluids are filtered before the analysis is done. Indometacin is very poorly soluble in gastric fluid, the solubility is only approximately 3 mg/l. Therefore only traces of dissolved indometacin are found in gastric fluid even if the particles are not sufficiently gastro-resistant. Therefore the test was modified following the Japanese Pharmacopoeia with 6 special cylindric baskets (17 mm ∅, height 23.5 mm) which were covered on either end with a sieve of 0.42 mm free-mesh distance (diameter of the wire 0.29 mm). These baskets were filled with the pellets, covered with the sieves and moved up and down in a DAB disintegration tester at 37 °C with the frequence of 30 lifts/min. In this apparatus all drug particles passing the sieve, which are smaller than 0.42 mm, are regarded as released. Under this condition we found, that all coated pellets, which are more than 0.6 mm ∅, remained intakt and release in simulated gastric fluid after 1 h was less than 3 %. After that the baskets were moved for 1 h in a buffer medium pH 5.0, where indometacin is soluble up to 13 $mg \cdot l^{-1}$. Also under this condition the coatings were undissolved, and the release of indometacin from coated pellets was below 3 % (Curve I, Fig. 14), with both coating formulations 8 and 9 in Table 1. Particles which were coated only with Eudragit L 30 D-55 show after compression to tablets an increase up to 10 % drug release after 2 h (curve II), but particles which were coated with the mixture of Eudragit L 30 D-55/Eudragit NE 30 D after tabletting show only less than 5 % drug release within 2 h (Curve III). At pH 6.8 and 7.2 in all cases very fast release and dissolution of the drug was observed.

2.3. *Scanning electron microscopic photos*

Scanning electron microscopic photos (SEM) were prepared after sputtering with gold for 20 min. The instrument was "Stereoscan" (Cambridge Scientific Instruments Ltd., Dortmund. FRG). Dimension and voltage is printed on any single photo.

2.4. *Strain-stress diagrams*

Strain-stress diagrams were prepared following DIN 53 455. Films 8 × 10 cm, 150–200 µm thick were formed by layering of 15 ml of the 30 % aqueous dispersions or mixtures on teflon-coated glass plates and drying 15 h at 40 °C. The films were equilibrated in an exsiccator at 50 % relative humidity minimum of 24 h at room temperature. Results of elongation at break see Table 6.

2.5. *Tap density and bulk density*

Tap density was measured according to DIN 53 194, bulk density according to DIN 53 912.

3. *Results and discussion*

On the SEM-photos especially Figs. 3 and 7 it is seen that the composition of fast disintegrating tablets is very similar to tablets made from drug granules where the granules form the inner phase and the excipients were mixed in a dry form to built

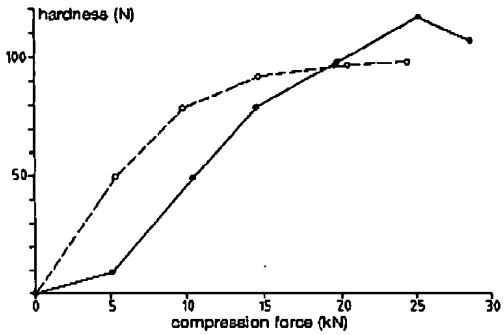

Fig. 15: Compressibility of KCl- (●) (Formula No. 1, Table 3) and ASA (○) powder mixtures (Formula No. 2, Table 3) for tabletting.

Table 6: Elongation at break of films from polymethacrylate dispersions (completed from [4]). Films were conditioned at 50 % relative humidity.

Eudragit types	Mixing ratio	Plasticizer (%)	Elongation at break (%)
L 30 D	-	10[a]	< 5
L 30 D	-	20[a]	14
RL 30 D	-	10[b]	30
RL 30 D	-	15[c]	150
RL 30 D	-	20[c]	300
RS 30 D	-	10[b]	40
RS 30 D	-	15[c]	80
RS 30 D	-	20[c]	250
NE 30 D	-	-	600
L 30 D/	9 : 1	10[d]	72
NE 30 D	8 : 2	10[d]	93
	7 : 3	10[d]	290
	5 : 5	10[d]	112
	3 : 7	10[d]	410

[a] Polyethylene glycol 6000, [b] triacetine, [c] triethyl citrate, [d] polysorbate 80.

up the outer phase of the system. These excipients have several functions: they reduce the friction of the larger particles and minimize their deformation by filling up the interspace. This can be seen well in the Fig. 6, 7 and 8 which show very clearly the layering of excipient particles between the coated particles. Moreover these excipients are also responsible for sufficient hardness and fast disintegration of the tablets after application.

As seen from Table 4 last column the time for disintegration was normally below 10 min, only with potassium chloride tablets (Formulation No. 2) it was up to 34 min what is also very short in comparison to the overall release time of 6 h.

Excipients for tabletting incorporated as the outer phase are preferably effective binders as microkristalline cellulose and common disintegrants as corn starch or sodium starch-glycolate, and also glidents as talc, magnesium stearate or others. The good compressibility of coated particles in mixture with these filling excipients leads to the formation of tablets of acceptable hardness with moderate compression forces: this can be seen in Fig. 15. With the compression force of 10 kN only a hardness of 50–80 N is obtained. Compression forces up to 15 and 25 kN gave hardness around 100 N.

The friction of powder particles in the tabletting mixtures can be measured by the ejection force. It was with all formulations very low in the range of 150–250 N. The amount of excipients, which is necessary to fill the interspace between the larger particles in a dense package of spheres is theoretically 29 % V/V. It is lower in the case of irregular particles, but we found earlier that an amount of less than 20 % of excipients will result in a strong increase of initial dose, caused by damage of coatings on the particles [4]. Obviously the amount of excipient must be so high that a separating layer is formed also around the surfaces of the coated particles to prevent adhesion or even confluence of the coatings.

Optimization of excipients in the outer phase of the tablet is in many cases not sufficient to protect coatings of usual composition, which are normally used in controlled release formulations for capsule filling. Only Eudragit NE 30 D with the elongation at break of approximately 600 % (Table 5) is flexible enough to follow deformation forces during tabletting: Formation of cracks or pores down to appr. 1 µm were not detected in scanning microphotos (see Fig. 8, 10 and 12).

The taste masking effect with paracetamol crystals remained after compression of coated particles. Also the release rate of coated potassium chloride-crystals was nearly unchanged.

When Eudragit NE 30 D is used in coating processes for sustained release, only variation of the thickness of the coating can be used to modify the release profile; addition of more hydrophilic or hydrophobic additives to the film are not effective and higher amounts of such excipients will influence the technical behaviour of the coating. So in most cases there is an unsufficient space for modifications to meet the technical as well as the pharmacological requirements. Several successful formulations were developed using Eudragit RL/RS mixtures. By the different permeability but unlimited miscibility of both typs, a wide range of permeability can be established, so that the system can be adapted to the diffusion properties of many drugs in a narrow range of film thickness. These polymers show unsufficient elongation at break of less than 50 % when no or only 10 % plasticizer is added. With more plasticizer of appr. 20 % calculated on polymer weight in the film, elongation at break increases up to 80–300 % (Table 5). We found that elongation at break of 75 % or more is sufficient for compression of coated particles without or with very small damage of the release controlling membrane.

Methacrylic acid copolymers as Eudragit L 30 D-55 used for enteric coatings are more brittle. Such films have elongation at break of appr. 20 % only independent of the film forming process from aqueous dispersions or organic solutions and here is no significant increase in flexibility if amount of plasticizer of normally 10–15 % is increased up to the level of 25–50 %. Such formulations are therefore of limited value in tabletting of coated particles. As seen in Fig. 11 with an example of ASA and in Fig. 14 with indometacin it can be seen that after compression of particles coated with Eudragit L 30 D-55 damage of coatings were detected, so that release in simulated gastric-fluid during 2 h was approximately 15–30 % from broken or perforated films. In scanning microscopic photos cracks of a length of more than 100 µm can be detected frequently. The width of these cracks was in the range of 5–50 µm (see Fig. 13). As long as the amount of cracks is limited so that not more than approximately 20–30 % of drug is released faster, it may be acceptable for retard formulations which contain already an initial dose in this range. But such preparations cannot meet the requirements of enteric formulations.

Fast disintegrating tablets releasing coated particles, which are resistant to gastric fluid to a very high extent can be prepared, when more flexible films are used in the coating process. Such films were obtained by mixing Eudragit L 30 D-55 and NE 30 D. As shown in Table 5 a mixing ratio of 1 : 1 will result in an elongation at break of the films of 112 % and a mixing ratio 8 : 2 together with 10 % polysorbate will give elongation at break of 93 %. As it can be seen from the results with ASA and indometacin such formulations are flexible enough, so that the tablets after fast disintegration as shown in Fig. 11 Curve III and Fig. 14 Curve III after 1 h treatment in gastric fluid or a

buffer of pH 5 less than 5 % of the drug is released: this limit seems to be acceptable and is also found in conventional gastro-resistant preparations as coated particles in capsules or even in coated tablets. When working very carefully in the coating and the tabletting process, preparations with only 1–2 % drug release per hour in gastric fluid can be prepared.

4. Conclusions

Coated particles of controlled drug release can be compressed to fast disintegrating tablets without significant deterioration of the release profile. To reduce the stress to the coatings during the tabletting process and to fill the interspace, admixture of about 20–50 % of usual tabletting excipients is useful: this will also give the desired fast disintegration of the tablets into the coated particles.

Additionally the formulations for the coating must be optimized to get films of sufficient flexibility. Eudragit NE 30 D, the aqueous dispersion of a methylmethacrylate-ethylacrylate copolymer, does not need addition of plasticizer, and films show high elongation at break of approximately 600 %. Eudragit RL 30 D and RS 30 D, copolymers of methylmethacrylate, ethylacrylate and trimethylammonioethylmethacrylate exhibit graded permeability and give films of sufficient flexibility after addition of approximately 20 % plasticizer, when elongation of break is above 75 %. Enteric coatings on the basis of Eudragit L 30 D-55, a methacrylic acid, ethylacrylate copolymer are brittle and not stable enough against compression forces, so that cracks are formed and 10–30 % of the drug released immediately in gastric fluid. By mixing Eudragit L 30 D-55 with the flexible Eudragit NE 30 D, enteric coatings of acceptable mechanical stability and sufficient flexibility can be prepared. When approximately 30 % of tabletting excipients including disintegrants are mixed together with the coated particles and compressed, the interspace is filled and the coatings are separated so that the tablets disintegrate rapidly and damage of particles and change of release profiles can be reduced to an insignificant level.

By using usual disintegrants the disintegration time can be kept down to a few minutes so that the released particles are mixed with the food contents and move continuously through the digestive tract. So tabletting of coated particles is an interesting alternative technology competing with the filling of hard gelatine capsules, and it is possible to make use of the general advantages of tablets for sustained release preparations as their higher drug concentration, safety against tempering, possibility to divide the dose and the inexpensive production technology.

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